REMARKS

Amendments to the Claims

Claims 19, 20, 23, 25, 26, 28-32 are pending in the present application, with claim 19 being independent. Applicant has amended claims 19, 25, and 29-32. No new matter is believed to have been added. Unless explicitly stated otherwise, none of the amendments to the claims were made for reasons substantially related to the statutory requirements for patentability. Furthermore, unless stated otherwise, the amendments to the claims were made simply to make express what had been implicit in the claims as originally worded and therefore are not narrowing amendments that would create any type of prosecution history estoppel.

Claim Rejections Under 35 U.S.C. § 112, first paragraph

Written Description

In the Office Action mailed January 6, 2012, the Examiner rejected claims 19, 20, 23, 25, 26 and 28-32 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. The Examiner alleges that the antigenic peptide of the instant claims is drawn to any peptide that is obtained from any amyloid protein and that the term amyloid encompasses other amlyoids without a structural relationship to Aβ. *Office Action* at 6 To further clarify the nature of the invention, claim 19 has been amended to make clear that the antigenic peptide is Aβ or an active fragment of Aβ. Claims 29 and 30 further specify that a portion of the Aβ fragment consists of a GXXXG or GXXXGXXGG motif. Applicant has provided 5 representative sequences (SEQ ID NOs: 1-5) of active fragments of Aβ. Further, the structure of Aβ was known at the time of the invention. Therefore, the genus of active fragments of Aβ is neither indefinite nor highly variant. An exact recitation of every member of the genus is not required. Accordingly, Applicants respectfully submit that given the knowledge of Aβ's structure and the five representative fragments disclosed, the present specification conveys with reasonable clarity to those skilled in the art that the Applicant was in possession of the claimed invention. Arguments regarding the failure to disclose any amyloid fragment not structurally related to Aβ are moot. For at least the foregoing reasons, Applicant submits the

present ground for rejecting claims 19, 20, 23, 25, 26 and 28-32 under 35 U.S.C. § 112 has been overcome, and respectfully request it be withdrawn.

Enablement

In the Office Action dated January 6, 2012, the Examiner further rejected claims 19, 20, 23, 25, 26 and 28-32 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Examiner acknowledges that the specification is enabling for a method of restoring memory and curiosity awakening by administering supramolecular antigenic constructs comprising a palmitoylated and pegylated antigenic peptide defined by SEQ ID NOs: 1-6, but does not reasonably provide enablement where the supramolecular antigenic constructs comprise any active fragment of amyloid or any peptides of GXXXGXXXGG or GXXXG motifs. *Office Action* at 2-3. Applicant's respectfully traverse the present ground for rejection.

The proper test for enablement is not that the specification bear an exact correlation to the scope of the claimed subject matter, but a **reasonable correlation** with the scope of the claimed subject matter.[1] Applicant respectfully submits that the application as filed provides guidance for making and using the presently claimed invention that bears a reasonable correlation to the administration of supramolecular constructs comprising Aβ or active fragments thereof.

Applicants provides five representative active Aβ fragments (SEQ ID NOs: 1-5) spanning the length of Aβ, including active fragments of Aβ wherein **a portion** of the fragment consists of a GXXXG or GXXXGXXXGG motif (SEQ ID NOs: 2, 3 and 4). Example 2 on pages 32-34 of the description provides detailed instructions on how to prepare the supramolecular antigenic constructs according to the to the presently claimed invention on the basis of three representative active Aβ fragments (4-11, 1-16, and 22-35).

Examples 3 and 7 provide results of a comparison of the immunogenicity of PEGylated and palmitoylated constructs and suitable assays known in the art (e.g. ELISA, disaggregation assay) that can be used in such a comparison. Example 4 provides results of a solubilization

assay for the Aβ 1-16 construct. Example 6 describes the production and characterization of monoclonal antibodies using three representative active Aβ fragments 1-16, 4-11, and 22-35. Also disclosed are the assay systems used for the characterization of the antibodies such as disaggregation assay and NRM studies.

Example 8 provides detailed protocols for evaluating the efficiency of the supramolecular constructs of the invention in various behavioral test systems such as the Morris Water Maze Test, Open Field Test, and Novel Object Recognition Test. The Applicant has shown based on three different active Aβ fragments (SEQ ID NO: 2, SEQ ID NO: 5, and SEQ ID NO: 3) that using the supramolecular constructs of the presently claimed invention significant immune responses can be obtained and antibodies produced which exhibit a high disaggregation activity towards amyloid fibers of up to 80% (see Table 1 on page 37) and are capable of inducing Aβ fibers to transition from a beta-sheet to an alpha-helix configuration. It is further taught, in the application as filed that antibodies obtained from mice immunized with the described construct display biological activity in APP {V717) FVB transgenic mice for human Alzheimer's Disease resulting in significant levels of memory restoration and of curiosity awakening without inducing bleeding in the brain of the immunized transgenic mice (see page 23, lines 15-22).

These specific properties of the antibodies produced using the presently claimed invention were confirmed in an additional mouse model (APPxPS1 mice) of Alzheimer as previously noted in Muhs *et al.* In particular, Muhs *et al.* confirmed the immune response induced by the unique antigenic constructs of the presently claimed invention translate into an increase of restored memory to levels comparable to healthy mice matched for age, gender, and genetic background upon administration of a representative embodiment of the presently claimed invention and testing the treated mice using the test systems disclosed in the present application.

It is the Applicant's understanding that the Examiner is of the opinion that this guidance is sufficient to support only constructs employing the explicitly disclosed sequences. Again, the test for enablement is not that the support provided have an exact correlation to the scope of the

[1] As long as the specification discloses at least one method for making and using the claimed invention that bears a **reasonable correlation** to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is

claims. Rather, the proper test is whether there is a reasonable correlation to the scope of the claims. Further, the description, and the guidance contained therein, is presumed enabling unless a reasonable basis can be established to question the enablement. *See* MPEP § 2164.04. To do so "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statements in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi,* 439 F.2d 220, 224 (CCPA 1971). The only evidence cited is the disclosure of Wolf-Klein *et al.* 24 AMERICAN JOURNAL OF HOSPICE & PALLIATIVE MEDICINE 77 (2007). The present grounds for rejection allege that Wolf-Klein discloses that the length of survival in Alzheimer patient's has not changed despite new technology and therapeutic approaches. *Office Action* at 3. The present grounds for rejection do not explain *why* this raises any factual basis for questioning the enablement of the presently claimed invention, nor is this acceptable reasoning. If, as acknowledged by the present grounds for rejection, administration of supramolecular constructs comprising the explicitly disclosed sequences are enabled in light of Wolf-Klein, it cannot be maintained that active Aβ fragments having a reasonable correlation to the explicitly disclosed fragments are not enabled. Further, Applicant is aware of no precedent establishing that the *status quo* of medical research is the controlling factor in assessing enablement. It is the very purpose of an invention to further technological advancement in order to find solutions to so far unresolved problems. Wolf-Klein itself acknowledges that such therapeutic advances have been and can be achieved in addressing Alzheimer's disease. Thus, there is nothing in Wolf-Klein that establishes that merely because a complete and total cure for Alzheimer's disease was lacking at the time that article was published, that therapeutic advances such as the ability to restore memory and curiosity awakening could not be predictably achieved.

Thus, Applicant respectfully submits the present ground for rejection fails to establish a reasonable basis to question the enablement of the presently claimed invention. No finding of fact has been provided as to why one of ordinary skill in the art could not take the known

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satisfied. *In re Fisher* F.2s 833, 839 (CCPA 1970).

structure of Aβ, the representative active fragments provided, and the disclosed methods for assessing an active fragment's activity relative to the disclosed sequences without engaging in undue experimentation. Accordingly, Applicant respectfully submits that that the level of direction and guidance in the specification bears a reasonable correlation to the scope of the claim, and that in light of such guidance one of ordinary skill in the art would not have to engage in undue experimentation in order to practice the full scope of the presently claimed invention. For at least the foregoing reasons, Applicant respectfully submits the present ground for rejecting claims 19, 20, 23, 25, 26 and 28-32 under 35 U.S.C. § 112, first paragraph, has been overcome and request that it be withdrawn.

New Matter

In the Office Action mailed January 6, 2012, the Examiner further rejected claims 29-32 as containing new subject matter. Specifically, the Examiner alleges that the phrases "wherein a portion of the B-amyloid fragment consists" in claims 29-30, and "hydrophobic moieties are fatty acids, trigylcerides, or phospholipids" in claim 31 constitutes new matter.

Regarding the phrase "wherein a portion of the B-amyloid fragment consists," Applicants note the present application discloses, for example, in Figure 5 SEQ ID NO: 2 and SEQ ID NO: 3 which are directed to fragments of Aβ, **a portion** of which consists of a GXXXG motif (SEQ ID NO: 2 – Ac-Lys-Arg(Pbf)-His(Trt)-Asp(OtBu)-Ser(tBu)-**Gly-Tyr(tBu)-Glu(OtBu)-Lys-Gly**-OH; SEQ ID NO: 3 – Ac-Lys-Glu(OtBu)-Asp(OtBu)-Val-**Gly-Ser(tBu)-Asn(trt)-Lys(Boc)-Gly-Ala-Ile-Ile-Gly-Leu-Met-Lys-Gly**-OH) and SEQ ID NO: 4, a portion of which consists of a GXXXGXXXGG motif (Ac-Lys-**Gly-Ala-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly**-Val-Val-Lys-Gly-OH). Accordingly, Applicants submits there is explicit support for the phrase wherein a portion of the β–amyloid fragment consist of a GXXXG or GXXXGXXXGG motif.

Regarding the phrase "hydrophobic moieties are fatty acids, trigylcerides, or phospholipids," claim 31 is amended wherein to recite wherein the fatty acid carbon backbones

comprise at least 10 carbons. Explicit support for claims 31 and 32 can be found on page 15, line 32 to page 16, line 2.

For at least the foregoing reasons, Applicants respectfully submit the present grounds for rejecting claims 29-32 under 35 U.S.C. § 112, first paragraph as containing new matter have been overcome and request they be withdrawn.

Claim Rejections Under 35 U.S.C. § 102

In the Office Action mailed January 6, 2012, the Examiner rejected Claims 19, 20, 23, 25, 26 and 28-32 under 35 U.S.C. § 102(b) as allegedly being unpatentable over Nicolau *et al.* 99 PNAS 2332 (2002). The Examiner alleges that Nicolau teaches administration of an antigenic composition comprising claimed SEQ ID NO: 1 in a reconstituted liposome comprising phospholipids and cholesterol in PBS, and that a hydrophobic tail is attached to the lysine residue of the peptide. The Examiner further alleges that because the identical antigenic composition is administered to a group of subjects having Aβ plaques, Nicolau's composition inherently enhances the antigenicity in a patient of Alzheimer's disease and thereby inherently anticipates the claim. Applicants respectfully traverse the present ground for rejection.

To inherently anticipate the presently claimed invention, the inherent characteristic, which in this case is the therapeutic effect of restoring memory and curiosity awakening in Alzheimer's patients suffering from Aβ plaque formation in the brain, must naturally flow from the explicit disclosure of Nicolau.[2] Inherency is limited to the four corners of the cited document and therefore the claimed therapeutic effect must naturally flow from administration of Nicolau's composition to NORBA mice.

The NORBA mouse model exhibits plaques in the pancreas and thus is a model for plaque-associated diseases of the pancreas such as Type-2 diabetes. Accordingly, the disclosure of Nicolau is strictly confined to studies of the pancreases of vaccinated and non-vaccinated NORBA mice. *Nicolau* at 2335, left column, second paragraph headed "Histochemical Studies."

[2] "A limitation or the entire invention is inherent and in the public domain if it is the '**natural result flowing from**' the **explicit disclosure** of the prior art." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1377 (Fed. Cir. 2005).

The doctrine of inherency does not allow an examiner to reach outside the bounds of the explicit disclosure of the cited reference and draw in additional inferences. Nicolau is silent about Aβ plaques on the brain. There is no evidence of record establishing that NORBA mice also suffer from the formation of Aβ plaques on the brain, or that acting upon Aβ plaque formation in/on the pancreas would result in memory restoration or curiosity awakening. Thus, restoring memory and curiosity awakening would not *naturally flow* from the administration of Nicolau's composition to NORBA mice. It is not sufficient that Nicolau's composition might restore memory and curiosity awakening if administered to a patient population with Aβ plaque formation in the brain. Rather, a patient population inherently suffering from Aβ plaque formation in the brain must be explicitly taught in Nicolau. As noted above this is simply not the case. For at least the foregoing reasons, Applicant respectfully submits the present ground for rejecting Claims 19, 20, 23, 25, 26 and 28-32 under 35 U.S.C. § 102(b) has been overcome and requests that it be withdrawn

No Waiver

All of Applicant's arguments and amendments are without prejudice or disclaimer. Applicant has not addressed each specific rejection of the independent and dependent claims because Applicant submits that the independent claims are allowable over the documents of record, as discussed above. Applicant has not acquiesced to any such rejection and reserves the right to address the patentability of any additional claim features in the future.

CONCLUSION

Applicant submits the foregoing as a full and complete response to the Official Action dated January 6, 2012. Applicant submits that this Amendment and Response places the application in condition for allowance and do not present any new issues for review by the Examiner. If any issues exist that can be resolved with an Examiner's Amendment or a telephone conference, please contact Applicant's undersigned attorney at 404.665.3099

Respectfully submitted,

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